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- a) [ensuring that said specimen contains an internal reference species (IRS) in a known concentration to calibrate all subsequent steps; whereby said specimen, upon being ensured that it contains an IRS, is referred to as an IRS-containing specimen;] combining said specimen with an internal reference species (IRS) of known concentration in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen;
- b) capturing and isolating said analyte and said IRS, wherein said capturing and isolating step comprises a substep of combining said IRS-containing specimen with an affinity reagent;
- c) quantifying said analyte in which said quantifying step comprises using mass spectrometric analysis to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal.

REMARKS

Claim Status

Claims 31-47 were pending. Claims 32, 34-39, and 42-47 were withdrawn from consideration. Thus, claims 31, 33, 40 and 41 are pending in the present application.

Declaration

The examiner has required a new oath or declaration because the oath or declaration submitted with the application was considered defective. The examiner states that the oath or declaration was invalid since the address of Inventor Krone was crossed out, but not initialed and no date of amendment was disclosed.

According to 35 U.S.C. 26 Effect of defective execution, any document to be filed in the Patent and Trademark Office and which is required by any law, rule, or other regulation to be executed in a specified manner may be provisionally accepted by the Commissioner despite a defective execution, provided a properly executed document is submitted within such time as may be prescribed.

The applicant is submitting another declaration by Inventor Krone, identifying this application by its serial number and filing date.

Specification

The examiner has required that the specification on page 1 should be amended to reflect the abandoned status of the parent application serial number 08/449,903.

The applicant has amended page 1 of the specification above to reflect the abandoned status of the parent application as required by the examiner.

Claim Rejections - 35 U.S.C. § 112

The applicant has rejected claims 31, 33, 40 and 41 as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, the examiner alleges that claims 31, 33, 40 and 41 recite the phrase "disposed in a specimen". The examiner alleges that this makes the claims confusing because it is not clear how the analyte is disposed in the specimen. The examiner cites examples such as "added to the specimen", "naturally occurring", "conjugated to another moiety", "analyte processed in some way". The examiner states that the instant rejection can be obviated by amending the claims to delete the term "disposed".

The applicant has amended claim 31 above to delete the term "disposed", thereby obviating the examiner's instant rejection by eliminating any confusion that could arise by inclusion of the word "disposed". Therefore, the applicant respectfully requests that the examiner withdraw the instant rejection.

The examiner has rejected claims 31, 33, 40, and 41 as being indefinite because claim 31 recites the phrase "ensuring that said specimen contains an internal reference species". The examiner alleges that the claim is confusing because the language is convoluted and difficult to understand. The examiner states that the instant rejection can be obviated by amending the claim to read "a) combining said specimen with an internal

reference species (IRS) of known concentration in order to calibrate all subsequent steps; whereby said combination is referred to as an IRS-containing specimen”.

The applicant has amended claim 31 above to replace the previous language in claim 31, subsection a) with the language suggested by the examiner. Therefore, the applicant respectfully requests that the examiner withdraw the instant rejection.

Claim Rejections - 35 U.S.C. § 102

The examiner has rejected claims 31, 33, 40 and 41 as being anticipated by van Ginkel et al. (J. of AOAC International, 1992, 75:554-560). Specifically, the examiner alleges that the claims are drawn to a method for quantifying an analyte in a specimen comprising combining an internal reference species (IRS) in a known concentration to calibrate all subsequent steps with the analyte in the specimen, capturing and isolating said analyte and IRS by combining them with an affinity reagent, quantifying said analyte using mass spectrometric analysis to resolve distinct signals for said analyte and said IRS to determine the ratio of the analyte signal to the IRS signal wherein said quantifying step further comprises using working curve analysis which comprises first obtaining a mass spectrum of a first portion of said IRS containing specimen then making a plurality of standard preparations each containing a known but differing amount of said analyte and each containing a known or equal amount of said IRS, then obtaining respective mass spectra of each whereby said respective mass spectra provide a working curve relationship of mass spectra relative to analyte concentration and then using said first mass spectrum and the standard preparation mass spectra working curve relationship to quantify said analyte.

The examiner alleges that van Ginkel et al., teaches a method for quantifying an analyte in a specimen comprising combining an IRS, an isotopically labeled internal standard for quantification and quality control (p. 55, col 1), in a known concentration to calibrate all subsequent steps with the analyte in the specimen (p. 556, col 1), capturing and isolating said analyte and IRS by combining them with an affinity reagent (p. 556, col 2) wherein the quantification of the analyte is determined by the ratio of the analyte to

the internal standard (that is the first mass spectrum of a first portion of the IRS containing specimen) and the quantification procedure used includes a linear calibration curve which is fitted with the ratio of abundance of the ions in question (i.e., tert-butyl-beta-agonists/internal standards) as the independent variable and the concentration of standard (ng/injection vial) as the dependent variable which procedure yields linear calibration curves with an intercept not significantly different than zero (p. 566, col 2) which inherently requires a plurality of standard preparations each containing a known but differing amount of said analyte and each containing a known or equal amount of said IRS to produce said linear calibration curve.

The van Genkel et al. document is interesting in the abstract. While van Genkel et al. discusses identifying analytes with mass spectroscopy; and van Genkel et al. discusses using immunoaffinity chromatography for sample cleanup, it is important to note that van Genkel et al. does not teach or disclose the claimed step of "capturing and isolating said analyte and said IRS, wherein said capturing and isolating step comprises a substep of combining said IRS-containing specimen with an affinity reagent". That is, van Genkel et al. does not teach or disclose the step of *simultaneous capture of the analyte and IRS*. What van Genkel does teach is the capture of an analyte using immunoaffinity chromatography (p 556, col 2, paragraphs 2 and 3). Van Genkel et al. teaches that the internal standard is added to an immunoaffinity chromatography elutant *after* the analyte has been isolated (p. 557, col 1, last paragraph wherein "During these experiments, the internal standard was not added in the beginning of the procedure but after the chromatography steps". Thus, not only does van Genkel et al., not teach or disclosed the claimed step, it teaches away from the claimed step by instructing experimenters to add internal standards after immunoaffinity chromatography capture.

Further, it appears that the van Genkel et al. document teaches the use of isotopically labeled standard. That is, the standard is the same compound being analyzed for, with the exception that some of the hydrogens are replaced with deuterium. Thus, for the van Genkel et al. method to work, one must know the identity of the analyte beforehand. In the present invention, no such limitation occurs. The internal standard,

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Atty. Docket No.: 530-005

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Examiner: Unger, S.

while capable of being the same compound as the analyte, need not be. Thus, the present invention is especially useful for the identification and quantitation of unknown analytes.

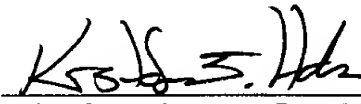
Therefore, since the van Genkel et al. document does not fairly teach or disclose the critical step of "capturing and isolating said analyte and said IRS, wherein said capturing and isolating step comprises a substep of combining said IRS-containing specimen with an affinity reagent", it does not anticipate the applicants invention. The applicant respectfully requests that the examiner withdraw the instant rejection and allow the claims to pass to issuance.

Conclusion

The applicant is submitting a new declaration for inventor Krone as required above. The applicant has amended the specification to correctly identify that the parent application has been abandoned. The applicant has amended claim 31 to obviate the examiner's section 112 rejections. The applicant has also explained and distinguished the van Genkel et al. document to show that it does not fairly anticipate the applicant's invention. Therefore, the applicant respectfully requests that the examiner withdraw all the rejections and allow the claims to pass to issuance.

Respectfully submitted,

Date: 2/29/00


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